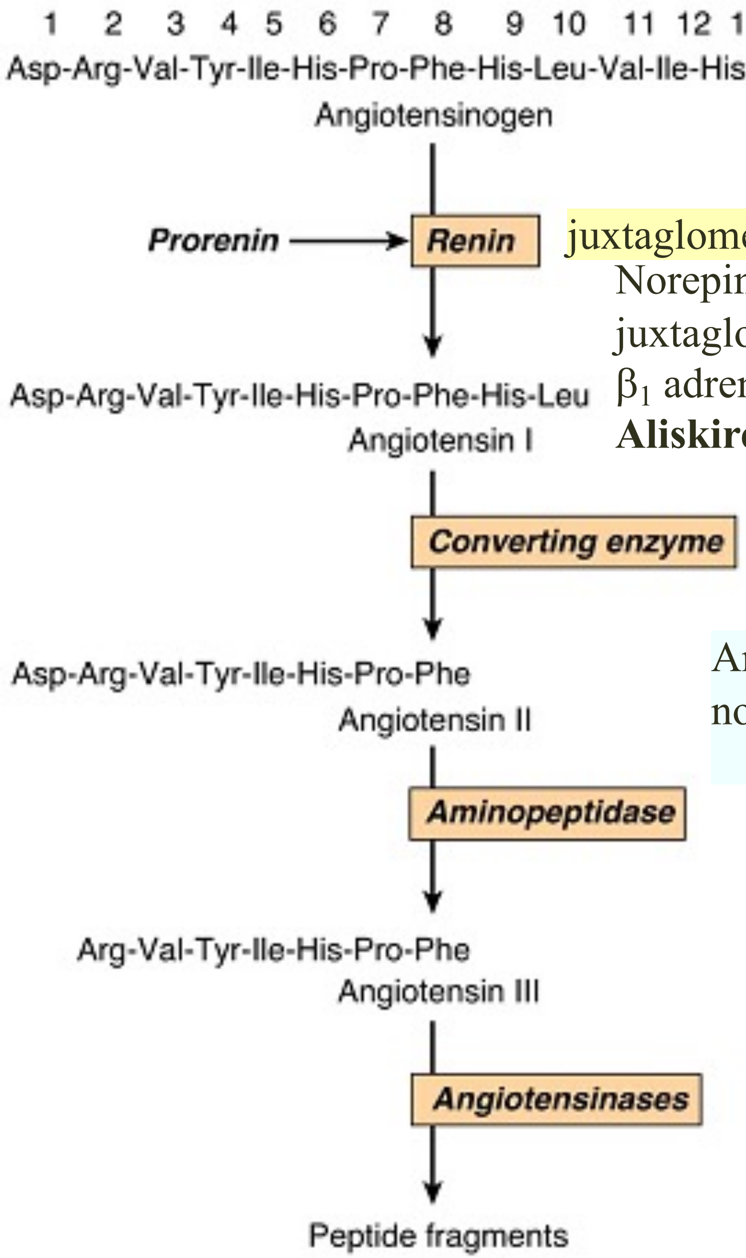
Chapter 17

Vasoactive Peptides

Vasoactive Peptides

- These peptides include
  - Vasoconstrictors
    - angiotensin II
    - Vasopressin
    - Endothelins
    - neuropeptide Y
    - urotensin
  - Vasodilators
    - Bradykinin
    - related kinins
    - natriuretic peptides
    - vasoactive intestinal peptide
    - substance P
    - Neurotensin
    - calcitonin gene-related peptide
    - adrenomedullin)

Angiotensin



juxtaglomerular cells: are the site of synthesis, storage, and release of renin.

Norepinephrine stimulates renin secretion by a direct action on the juxtaglomerular cells. In humans, this effect is mediated by β_1 adrenoceptors.

Aliskiren: suppresses plasma renin activity

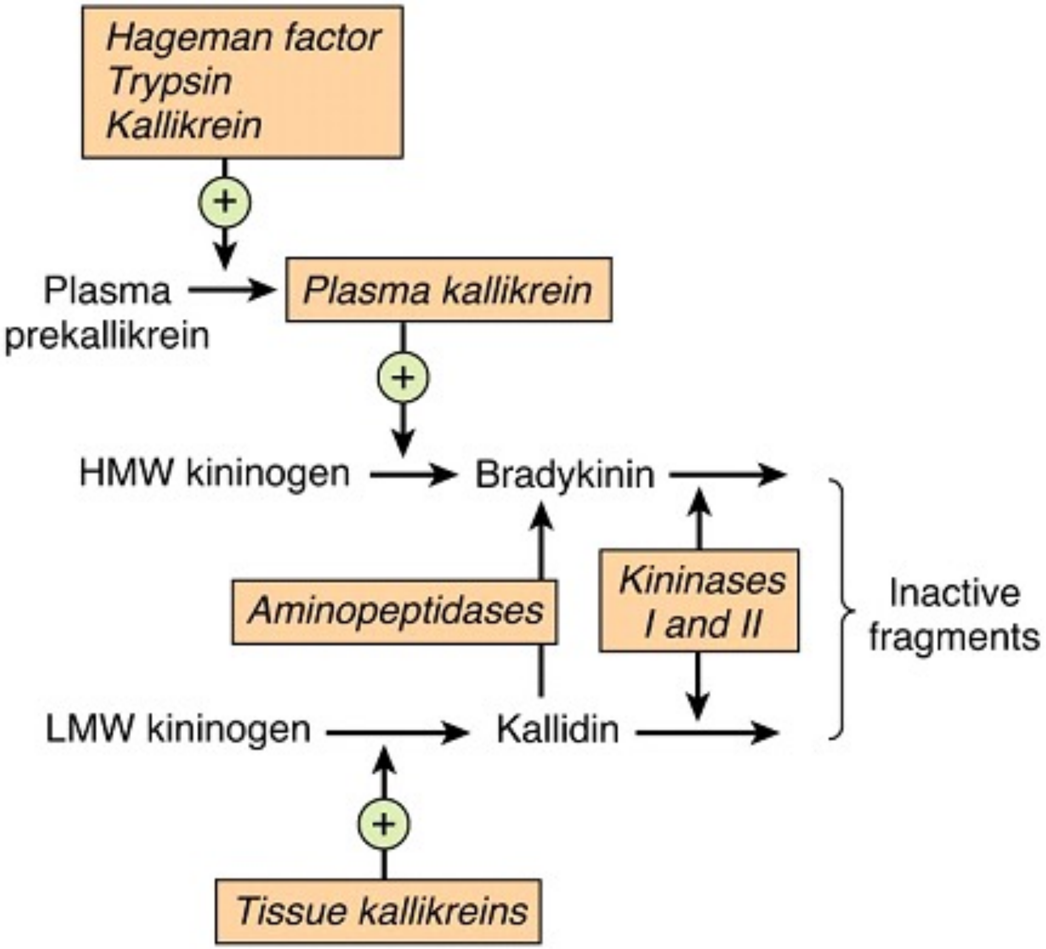
Captopril and enalapril

Ang II receptor blockers (ARBs): saralasin (peptide).

non peptide ARBs: Losartan, valsartan, eprosartan, irbesartan, **candesartan**, olmesartan, and telmisartan

Kinins

- Kinins: potent vasodilator peptides
  - Three kinins have been identified in mammals
    - Bradykinin
    - lysylbradykinin (also known as kallidin)
    - methionyllysylbradykinin



Physiologic & Pathologic Effects of Kinins

- Effects on the Cardiovascular System
- Effects on Endocrine & Exocrine Glands
- Role in Inflammation
- Effects on Sensory Nerves
- Other Effects
  - bradykinin may play a beneficial, protective role in certain cardiovascular diseases and ischemic stroke-induced brain injury

Kinin Receptors & Mechanisms of Action

- Two types of kinin receptors, termed B_1 and B_2, have been defined based on the rank orders of agonist potencies.
  - Note that *B* here stands for bradykinin, not for β-adrenoceptor
    - B_1 receptors
      - appear to have a very limited distribution in mammalian tissues and have few known functional roles.
    - B_2 receptors
      - are G protein–coupled and agonist binding sets in motion multiple signal transduction events, including calcium mobilization, chloride transport, formation of nitric oxide, and activation of phospholipase C, phospholipase A_2, and adenylyl cyclase.

Icatibant

- Mechanism
  - B_2 receptor antagonist.
- Actions
  - Icatibant has been used extensively in animal studies to block exogenous and endogenous bradykinin and in human studies to evaluate the role of kinins in pain, hyperalgesia (高敏感度疼痛) , and inflammation.
- Indications
  - It shows promise for use in the treatment of hereditary angioedema and pain.

Vasopressin

- Vasopressin (**antidiuretic hormone, ADH**)
  - plays an important role in the long-term control of blood pressure through its action on the kidney to increase water reabsorption.
- Three subtypes of vasopressin receptors
  - **V_1 receptors**
    - **V_{1a} receptors** mediate the vasoconstrictor action of vasopressin
    - **V_{1b} receptors** potentiate the release of ACTH by pituitary corticotropes
  - **V_2 receptors** mediate the antidiuretic action

Terlipressin

- Mechanism
  - V_1 receptor agonist
- Actions
  - A synthetic vasopressin analog that is converted to lysine vasopressin in the body
  - It may have advantages over vasopressin because it is more selective for V1 receptors and has a longer half-life
- Indications
  - Bleeding esophageal varices (食管靜脈曲張)
  - 第一型肝腎症候群
- Side effects
  - Abdominal cramps; headache; transient blanching; increase in arterial BP

- Conivaptan
  - Mechanism
    - V_1 receptor antagonist
  - Actions
    - Vasodilation
  - Indications
    - Potential use in hypertension and heart failure hyponatremia (低鈉血症)
  - Side effects
    - hypotension

Natriuretic Peptides

- The atria and other tissues of mammals contain a family of peptides with natriuretic, diuretic, vasorelaxant, and other properties
  - The family includes
    - Atrial natriuretic peptide (ANP)
    - Brain natriuretic peptide (BNP)
      - **nesiritide**
    - C-type natriuretic peptide (CNP).

Nesiritide

- Mechanism
  - BNP receptor agonist
- Actions
  - Increased sodium and water excretion
  - vasodilation
- Indications
  - Heart failure
- Side effects
  - Renal damage
  - hypotension

Endothelins

- The endothelium is the source of a variety of substances with vasodilator (PGI_2 and nitric oxide) and vasoconstrictor activities.
  - Structure
    - **ET-1**
      - central nervous system, renal mesangial..
    - **ET-2**
      - kidneys and intestine
    - **ET-3**
      - brain
  - Receptors
    - **ET_A** Receptor
      - vasoconstriction
    - **ET_B** Receptor
      - release of PGI2 and nitric oxide

Bosentan

- Mechanism
  - ET_A and ET_B receptor antagonist
- Actions
  - Vasodilation
- Indications
  - Pulmonary hypertension
- Side effects
  - Hepatic impairment; possible teratogen (致畸胎)

Substance P

- tachykinin family of peptides
  - Substance P (the most important)
    - In the central nervous system
    - In the gastrointestinal tract
  - Neurokinin A
  - Neurokinin B

mediated by **NK$_1$** , **NK$_2$** , and **NK$_3$** receptor

behavior, anxiety, depression, nausea, emesis, potent vasodilator…

- Aprepitant (Emend®)
  - Mechanism
    - Tachykinin NK_1 receptor antagonist
  - Actions
    - Blocks several central nervous system effects of substance P
  - Indications
    - Antiemetic for chemotherapy-induced vomiting
  - Side effects
    - Asthenia, hiccups

      (無力，打嗝)

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